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### Missing Link?: Alachlor and Semen Quality

The article by Swan et al. (2003) suggested that alachlor exposure was linked to reduced sperm quality in fertile men; after publication of the article, Monsanto (St. Louis, MO) began a detailed examination of the issue because the findings were entirely unexpected and inconsistent with both our information and the extensive published literature on alachlor. Most surprisingly, alachlor mercapturate (AM) was reportedly found in the urine of 92% of study participants in Columbia, Missouri. Because this metabolite arises exclusively from exposure to the parent compound, few, if any, detects would be expected based on declining alachlor use (National Agricultural Statistics Service 2005) and our detailed understanding of its biological and environmental properties (Feng et al. 1994). Also, extensive water monitoring studies submitted to the U.S. Environmental Protection Agency (EPA) have shown that parent alachlor occurs very infrequently in both potable wells (Holden et al. 1992) and drinking water from surface water sources (Hackett et al. 2005), thereby calling into question the plausibility of such widespread exposure.

We met with Swan and colleagues at the University of Missouri in Columbia (UMC), and with the personnel at the Centers for Disease Control and Prevention (CDC) who conducted the analyses, to discuss our surprise at the findings. Our concern about the reported frequent detections of alachlor in urine was heightened when we learned that the liquid chromatography/mass spectrometry–mass spectrometry method employed by the CDC (Olsson et al. 2004) included no confirmatory ions, a standard technique for avoiding false positives in the analysis of urine (Department of Health and Human Services 1998). An 18-month collaboration ensued, which included numerous discussions and a round-robin study conducted between Monsanto and the CDC, with involvement by UMC researchers, to assess the performance and transferability of the methods used by each laboratory.

After successful completion of the round-robin study, several frozen urine samples retained from the original study were sent to Monsanto. In results that we intend to submit for publication, we found no detectable level of AM (limit of detection < 0.10 ppb) in samples that the CDC reported to contain up to 3 ppb (Swan et al. 2003). Sample

degradation does not explain this difference, because we have data demonstrating AM stability under such conditions. Our analyses followed Good Laboratory Practice standards [U.S. Environmental Protection Agency (EPA) 1989] and included confirmatory ions. We also analyzed urine samples of 52 volunteers from agricultural areas across North America, none of which actually contained detectable AM, but 11 of which showed false positives when confirmatory ions were not used.

The CDC has now modified its method to include confirmatory ions for alachlor. We are confident that little or no AM would have been detected had they included confirmatory ions in the original analysis. The CDC previously declined Monsanto's request that they analyze the original samples using a modified method with confirmatory ions. However, after receiving an earlier version of this letter, the CDC quickly performed new analyses of 14 retained frozen samples and informed us that analysis with confirmatory ions validated their original findings. Unfortunately, the CDC has not provided us with sufficient data to confirm the validity of the new method and results. Monsanto continues to believe the detections are spurious. From our perspective, the only possible resolution of the matter at this time would be for the retained samples to be sent to an independent third-party laboratory for confirmatory analysis.

We understand Swan et al. are now having urine samples from other similar agricultural areas analyzed using a confirmatory method, and that AM is no longer being routinely detected. This would affirm that alachlor exposure is rare and the alleged link to semen quality is implausible. It would be very informative to identify the apparent interferent using high-resolution mass spectrometry methodology, but our collaboration has clearly shown that it was not AM. The evidence presented by our analyses of the samples provided by Swan, supported by our successful performance in the round-robin analysis of fortified samples, demonstrates that the reported detections of alachlor were most likely attributable to an interferent. The data refute any link between alachlor exposure and reduced sperm quality in fertile men.

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*Editor's note: Swan et al. chose not to respond because the criticism was aimed at the CDC; see Barr's response below.*

### Missing Link: Barr and Needham Respond

In January 2004, the Monsanto Company contacted our laboratory at the Centers for Disease Control and Prevention (CDC) regarding their concern about the association between alachlor (a Monsanto product) exposure and semen quality reported by Swan et al. (2003). As a result, we provided Monsanto with detailed information about our methodology for alachlor exposure assessment by measuring its urinary metabolite alachlor mercapturate (AM). In addition, we participated in a study in which Monsanto sent 25 urine samples to the CDC for analysis. Monsanto had spiked 15 of these samples with AM (< 1.5 ng/mL), and 10 unspiked samples were collected from a field study; all were blinded to the CDC. We did not detect AM (> 0.1 ng/mL) in any of the field samples, including one with an alleged interferent; thus, the method did not produce false-positive results. For the spiked urine samples, the CDC and Monsanto measurements showed excellent correlation ( $r = 0.9881$ ;  $p < 0.0001$ ), although the Monsanto measurements averaged about 30% higher. Similarly, the CDC sent samples representing a broader range of concentrations (~ 1–100 ng/mL) to Monsanto for blinded analysis; again, the results were comparable.

At Monsanto's request, residual samples from those originally tested by Swan et al. (2003) were sent to them for analysis.

Because of sample volume constraints, Monsanto pooled individual samples to produce three samples with concentrations of < 0.1 ng/mL, approximately 0.2 ng/mL, and approximately 3 ng/mL. Monsanto did not detect AM in any of the pooled samples; thus, they concluded that the CDC obtained false-positive results possibly caused by a putative interferent. We suggested that Monsanto use the CDC method in its laboratory to assess whether they observed the interferent. Although Monsanto originally agreed to do this, they reportedly did not do so.

The addition of confirmation ions does increase confidence in measurements, although the method used by Swan et al. (2003) was peer-reviewed, published in *Analytical Chemistry*, and included many components that produce highly reliable results (Olsson et al. 2004). We have since acquired technology that allowed us to measure AM with a similar limit of detection while including confirmation ions. Using both the older method (Olsson et al. 2004) and a newer one (Norrgran et al., in press), we analyzed 14 properly archived samples that were split from samples originally analyzed and reported by Swan et al. (2003) and compared all data. In these samples, the AM levels were similar to those previously obtained ( $r = 0.9912$ ;  $p < 0.0001$ ) (Norrgran et al., in press) and showed good agreement using either method ( $r = 0.9999$ ;  $p < 0.00011$ ) (Norrgran et al., in press). We recently shared with Monsanto chromatograms of a urine sample with low levels of AM as determined by all three analyses and provided sufficient information with which to evaluate the methodology. Furthermore, we offered to discuss these new results with Monsanto, but they have not accepted this offer.

Finding AM concentrations in urine samples collected in 2000 from men in Missouri is not unlikely. Several studies have detected alachlor with high frequency in Midwestern groundwaters and surface waters (Battaglin et al. 2000; Lerch and Blanchard 2003) near the time and location our sampling occurred. Thus, although we do not frequently detect AM in general population samples, we were not surprised to find it in urine samples collected from this region. Also, contrary to Gustafson's claim, we have not yet analyzed any field samples from other agricultural areas using our new method.

We strive to present quality human exposure assessment data. We have been assessing alachlor-related exposures since 1994; in fact, we were the first to report that AM was the primary human metabolite of alachlor (Driskell et al. 1996). Our laboratory uses

both the highest caliber instrumentation and isotopically labeled internal standards, which result in high-quality, validated exposure-assessment methods capable of producing reliable and consistent results. Furthermore, our laboratory is certified to analyze human biological samples according to the Clinical Laboratory Improvement Amendment (1988), which requires extensive quality control and assurance, semiannual blinded proficiency testing, continued verification and documentation of operational parameters, and recertification every 2 years.

We do not know why Monsanto did not obtain similar results when analyzing pooled urine samples left over from the original analyses. Possible false-negative analyses could result from multiple confirmation ions that limit the sensitivity of detecting low concentrations, degradation of AM in the samples that had undergone several thaw-freeze cycles, or inadvertent dilution of AM during the pooling process. However, the results from our analysis of properly archived specimens from 14 of the same persons from the original study provide strong evidence that our first analyses were, indeed, correct. Perhaps, when we have more details on Monsanto's methodology and sample handling procedures, we can further explore potential reasons for the discrepancy between our results.

*The authors declare they have no competing financial interests.*

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## Vinyl Chloride and U.S. EPA Research

A commentary by Sass et al. (2005), "Vinyl Chloride: A Case Study of Data Suppression and Misrepresentation," is itself a case study in misrepresentation. The inclusion of such an article in this peer-reviewed publication stands in contrast to its stated mission to publish "balanced" and "objective" information. Sass et al. (2005) did not include or address recent studies in characterizing the weight of the scientific evidence related to vinyl chloride and made inaccurate and unsupported allegations about the integrity of U.S. Environmental Protection Agency (EPA) scientists and the rigorous peer review process utilized by the U.S. EPA.

Sass et al. (2005) asserted that there is a "scientific consensus that [vinyl chloride] is a multisite carcinogen in humans and experimental animals," referencing 21 articles, only 3 of which were published during the past 15 years. They failed to mention or seriously discuss 7 articles noted below that were published in scientific journals since 1997 and update many of the studies Sass et al. cited and reach the opposite conclusion. These and other recent peer-reviewed studies and reviews fully support the U.S. EPA's conclusion that "the association [between vinyl chloride and cancers other than the liver] is weak and any estimated increase in mortality from cancer at these sites is likely to be less than for liver cancer" (U.S. EPA 2000).

Authors of these articles include Aaron Blair, the chief of the Occupational Studies Section of the National Cancer Institute (NCI), who stated that epidemiologic evidence shows a strong exposure-response relationship for angiosarcoma of the liver, but not for other types of cancer (Blair and Kazerouni 1997). In a more recent review, McLaughlin and Lipworth (1999) reached the same conclusion:

Occupational vinyl chloride exposure has not been conclusively causally linked to any adverse health outcome, with the exception of angiosarcoma of the liver.

Even more recently, Bosetti et al. (2003) stated that

The aggregate data are reassuring in excluding any excess risk of death from lung, laryngeal, soft tissue sarcoma, brain and lymphoid neoplasms, as well as cirrhosis.

Recently published updates of cancer incidence in European and American industry-wide cohorts of workers exposed to vinyl chloride provide a firm basis for the conclusion that vinyl chloride exposure is not causally associated with brain cancer and the other tumors mentioned by Sass et al. (2005). The European study (Ward et al.

2001) was conducted by scientists affiliated with the National Institute of Occupational Safety and Health (NIOSH) and the International Agency for Research on Cancer (IARC). The authors found no evidence of an increase in cancers other than the liver. Similar, though less definitive, results were published by Mundt et al. (2000) in an update of the American cohort. A recent meta-analysis of these cohorts by IARC scientists further supports the conclusion reached by the U.S. EPA (Boffetta et al. 2003).

Given the strength and uniformity of the evidence supporting the U.S. EPA's position, it is striking that Sass et al. (2005) did not address it. Instead, they claimed that the U.S. EPA yielded to advocacy by chemical manufacturers, implying that the U.S. EPA relied in part upon unpublished data. As noted above, however, the articles upon which the U.S. EPA placed primary reliance are published, in a few cases, by academic scientists sponsored by industry (e.g., Mundt et al. 2000), but for the most part by scientists affiliated with some of the most prestigious government-supported organizations engaged in cancer research (e.g., NCI, IARC, NIOSH).

Finally, it is not accurate that industry unduly influenced the review process for vinyl chloride nor that the potency factors published in the IRIS (Integrated Risk Information System) database (U.S. EPA 2000) are insufficiently protective (Norman 2002). The former comment disparages the U.S. EPA scientists who spent 5 years and went through two external peer reviews to make sure that relevant current science was reflected. The latter fails to recognize that a pharmacokinetic (PK) approach to risk assessment was supported over 20 years ago by the National Academy of Sciences and that the PK model for vinyl chloride used by the U.S. EPA—which predicted the actual incidence of angiosarcoma of the liver in the early cohorts of exposed workers—has been peer-reviewed, published, and validated (Clewell et al. 2001; Reitz et al. 1996).

*The author is employed by the American Chemistry Council, a trade association representing the chemical industry, including manufacturers of vinyl chloride. The author has had, may have, or may in the future have investment interests in chemical companies, but does not consider these to constitute competing financial interests.*

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## Vinyl Chloride: Sass et al. Respond

We provided documentation and extensive references to support two claims: industry urged the U.S. Environmental Protection Agency (EPA) to downplay data suggestive of cancer risks in tissues other than the liver, and the U.S. EPA reduced the cancer potency estimate of vinyl chloride in accordance with industry input. The American Chemistry Council (ACC) is a trade association representing over 150 companies that produce and use chemicals, including the Dow Chemical Company (Midland, MI), Georgia Gulf Corporation (Atlanta, GA), and Occidental Chemical Corporation (Los Angeles, CA) (ACC 2005). These three companies are also full members of the Vinyl Institute (Arlington, VA), whose stated goal is to “promote and protect the vinyl industry and the markets it serves” (Vinyl Institute 2005). Price, a lawyer with the ACC, maintains that our commentary is inaccurate because *a*) studies published since 1997 “reach the opposite conclusion”; *b*) by demonstrating industry influence on the U.S. EPA assessment of vinyl chloride we are disparaging of U.S. EPA scientists; and *c*) the pharmacokinetic (PK) model used by the U.S. EPA has been “peer-reviewed, published, and validated.”

In response to Price's first point, recent studies confirm earlier findings instead of the opposite. At the time of the U.S. EPA assessment (U.S. EPA 2000) there were over 20 scientific articles and two independent reviews by the International Agency for Research on Cancer (IARC 1979, 1987) suggesting that vinyl chloride is a multisite carcinogen in humans and experimental animals. Recent reviews and data support the IARC conclusions. Of the references listed by Price, three are reviews without new data (Blair and Kazerouni 1997; Boffetta et al. 2003; Bosetti et al. 2003), two describe a PK model (Clewell et al. 2001; Reitz et al. 1996), and two contribute new data that neither refute previous studies nor support ACC claims (Mundt et al. 2000; Ward et al. 2001). One of these is a North American multicenter investigation, discussed in our commentary, which reported modest “excesses of brain cancer” and “cancer of connective and soft tissue” (Mundt et al. 2000). The second new study is a European multicenter investigation that is inconclusive regarding risks of nonliver cancers (Ward et al. 2001). Price also references a meta-analysis that actually reported an excess in brain cancer [standardized mortality ratio (SMR) = 1.26; 95% confidence interval (CI), 0.98–1.62] and soft-tissue sarcomas (SMR = 2.52; 95% CI, 1.56–4.07) (Boffetta et al. 2003); the authors of this meta-analysis concluded that “increased mortality from lung and brain cancers and from lymphatic and hematopoietic neoplasms cannot be excluded.” This is consistent with an Italian study that reported increased lung cancer deaths among polyvinyl chloride (PVC) baggers (RR = 3.04; 95% CI, 1.15–7.99) (Gennaro et al. 2003).

Price's letter and the U.S. EPA assessment (U.S. EPA 2000) both reference a review article by National Cancer Institute authors (Blair and Kazerouni 1997). Blair stressed that his findings do not support disregarding possible risks of cancer outside the liver and that potent carcinogens such as vinyl chloride are unlikely to affect only one organ site (Blair A, personal communication). In overall mortality, a slightly increased rate of a common cancer such as lung cancer may lead to more deaths than a more markedly increased rate of a rare cancer such as liver angiosarcoma.

We believe that the U.S. EPA's close relationship with industry compromises credibility. The ACC met with U.S. EPA regulators to discuss a vinyl chloride assessment at least 2 years before public notification of an assessment process. At the urging of the ACC (Price 1999), the U.S. EPA eliminated a statement that there is “suggestive epidemiological evidence that cancer of

the brain, lung, and lymphopoietic system” associated with vinyl chloride exposure. The U.S. EPA also removed a 3-fold uncertainty factor that had been included to account for possible tumor induction at such sites, after an ACC letter called the factor “ill advised” (Price 1999). The result is that the U.S. EPA assessment (U.S. EPA 2000) does not adequately warn the public of the potential carcinogenicity of vinyl chloride suggested in the scientific literature, and the risk estimate is weakened 3-fold.

The PK model has not been validated, as stated by Price. The PK model developed by industry consultants and used by the U.S. EPA in its assessment has not been validated because assumptions used in the model have not been tested. Importantly, although the model is limited to liver effects only, the implicit assumption that all metabolism occurs in the liver is incorrect (IARC 1987; McFayden et al. 1998; U.S. EPA 2000).

By using a model limited to liver cancer, the U.S. EPA made a radical departure from its cancer guidelines, recommending that the cumulative risks of all tumor types be included in a cancer assessment (U.S. EPA 1999, 2005). The 1999 carcinogen guidelines under which vinyl chloride was assessed (U.S. EPA 1999) state that

In the analysis of animal bioassay data on the occurrence of multiple tumor types, the cancer potencies should be estimated for each relevant tumor type that is related to exposure, and the individual potencies should be summed for those tumors.

This inclusive approach is reconfirmed in the 2005 guidelines (U.S. EPA 2005). This protective approach was not taken by the U.S. EPA in its assessment of vinyl chloride cancer risks.

*J.B.S. and D.W. are employed by environmental nonprofit organizations with an interest in ensuring that regulations of toxic chemicals are as health protective as feasible. B.C. is an independent consultant in toxic substances control and has no competing financial interests regarding the subject matter of this letter.*

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## Risk-Based Consumption of Dioxin-Contaminated Farmed Salmon

In their article, “Risk-Based Consumption Advice for Farmed Atlantic and Wild Pacific Salmon Contaminated with Dioxins and Dioxin-like Compounds,” Foran et al. (2005) present recommendations for consumption of salmon containing dioxin-like compounds (DLCs) based on three risk assessment approaches.

Relying strictly on risk assessment to develop fish consumption advice has many

shortcomings and may actually do more harm than good (Arnold et al. 2005; Egeland and Middaugh 1997). Risk assessment is only part of the risk management process when developing fish consumption advice [U.S. Environmental Protection Agency (EPA) 1996]. Other factors need to be considered when developing fish consumption advice, such as the nutritional and health benefits of consuming fish and the cultural, societal, and economic impacts of reduced fish consumption (U.S. EPA 1996). Ignoring these factors may place an undue burden on a local population by removing a relatively inexpensive protein source that would likely be replaced by a less healthy substitute (Arnold et al. 2005; Egeland and Middaugh 1997). Decisions to limit fish consumption should only be made at the local level because local public health officials are most aware of the local aforementioned impacts and the actual concentration of contaminants in locally caught fish [Arctic Monitoring and Assessment Programme (AMAP) 2002; Arnold et al. 2005; Hites et al. 2004].

In addition to measuring contaminant concentrations in fish, human biomonitoring is a very useful tool to measure actual levels of contaminant exposure in targeted “at-risk” populations rather than relying solely on calculated estimates of exposure. Biomonitoring should ideally be performed in any identified at-risk population to verify that a problem actually exists before advising people to reduce fish consumption. This is especially true in populations that rely on locally caught fish as their primary protein source and that have few inexpensive healthy alternatives. Fortunately, recent evidence suggests that the average concentration of DLCs in the general U.S. population is declining (U.S. EPA 2000).

Two aspects of this study’s (Foran et al. 2005) methodology are problematic because they lead to inappropriately conservative estimates of health risk. First, the majority of people in the United States do not eat salmon skin, and as the authors noted, cooking has been shown to reduce DLCs in fish tissue. Because DLCs partition to fatty tissues including skin, measuring DLCs in raw fish with the skin on will overestimate the amount of exposure to DLCs and overestimate the consumption risks. Second, when assessing health risks posed by salmon consumption, Foran et al. (2005) estimated the number of meals of salmon per month that would limit dioxin intake to 20% above the U.S. average “background” adult intake level of 65 pg toxic equivalents (TEQ)/day. This approach ignores the fact that the background rate incorporates both freshwater and saltwater fish consumption (U.S.

EPA 2000). In effect, Foran et al. (2005) double counted dioxin exposure through fish consumption. They also ignored the fact that a person who chooses not to consume a salmon meal would likely substitute another protein source that also contains trace quantities of DLCs.

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## Dioxin-Contaminated Farmed Salmon: Foran et al. Respond

Middaugh et al. suggest that relying strictly on risk assessment to develop fish consumption advice has many shortcomings. We agree. They also argue that risk assessment is only part of the risk management process. Although we separate risk assessment and risk management, we agree conceptually that risk management decisions often must be based on more than just the results of a quantitative risk assessment.

What Middaugh et al. fail to recognize is that our report on dioxins in salmon (Foran et al. 2005) was not intended to serve as a fish consumption advisory. Such advisories should be left to appropriate state, federal, and international organizations charged with protection of public health. Rather, we reported risk-based consumption advice that would be triggered by dioxin-like compounds (DLCs) in farmed Atlantic and wild Pacific salmon using two different

approaches; the World Health Organization (WHO) tolerable daily intake (TDI) for DLCs and a margin-of-exposure approach advocated by the U.S. Environmental Protection Agency (EPA 2002). We also reported cancer risks, based on the proposed U.S. EPA cancer slope factor for DLCs (U.S. EPA 2002) that would be generated at particular salmon consumption levels. Our results demonstrate clearly that consumption of some farmed Atlantic salmon, even at relatively modest levels, raises human exposure to DLCs above the lower end of the WHO TDI and considerably above background DLC intake for adults in the United States. Further, consumption at these levels poses elevated cancer and noncancer health risks.

Middaugh et al. suggest that human biomonitoring should be used rather than relying on calculated estimates of exposure, presumably to generate fish consumption advice. We strongly disagree, particularly in the case where the exposure source (farmed Atlantic salmon) is not localized. This is a global problem that would require human biomonitoring on immense temporal and spatial scales. In this case, quantitative risk assessment, which includes an assessment of chemical fate, transport, exposure, and effects, is an appropriate surrogate for human biomonitoring. Further, given our vast knowledge of the toxicokinetic behavior and toxicologic effects of dioxin and other bioaccumulative compounds in farmed Atlantic salmon, requiring human biomonitoring before issuing consumption advice is akin to continuing a clinical trial of a drug where unacceptable adverse effects have already been demonstrated. Clearly, responsible public health professionals should strenuously object to such an approach.

Middaugh et al. suggest that two aspects of our study are problematic. First, they argue that measuring contaminants in skin-on fillets may overestimate contaminant concentrations in edible fish tissue and, ultimately, human exposure. We addressed this issue in our article (Foran et al. 2005). We encourage Middaugh et al. to reexamine our conclusion that most studies of the effects of preparation (including removal of skin) and cooking on contaminant concentrations in fish tissue

suffer from small sample sizes, questionable data analyses, inconsistent analytical techniques, inconsistent data presentation, and variability in initial and postintervention contaminant concentrations within and among species, preparation techniques, and cooking techniques. Deficiencies in study design and variability in contaminant reductions preclude development of a useful quantitative correction factor for the effects of preparation and cooking on contaminant burden. As a result, reductions in exposure and risk associated with reduction in contaminant concentrations from

preparation and cooking cannot be evaluated quantitatively; thus, we have not incorporated the effects of cooking and preparation in our risk assessments.

Second, Middaugh et al. are correct in stating that we did not adjust for the existing background concentration that incorporates DLC exposure via fish consumption. However, we did assess such exposures and concluded that they were so low, compared with exposure to DLC through consumption of farmed Atlantic salmon, as to be inconsequential in our risk assessment calculations.

Finally, we regret that Middaugh et al. ignored two critically important conclusions of our work. First, in all of our articles (Hites et al. 2004a, 2004b; Foran et al. 2004, 2005) that address contamination of salmon sold commercially, we provided information that will allow and encourage consumers to choose other fish, including wild Pacific salmon, as well as other sources of beneficial n-3 fatty acids. Second, our work has exposed serious deficiencies and inconsistencies in national and international approaches to the management of contaminants in commercially sold fish. These deficiencies and inconsistencies must be resolved so that consumers can confidently choose and consume fish with lower contaminant concentrations while continuing to accrue the health benefits of fish consumption.

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## Disease and “Broken Windows”

Frumkin’s editorial in the May 2005 issue of *EHP* (Frumkin 2005) was very interesting and enlightening. On page A291, Frumkin cited several studies that endorse the “broken windows theory,” noting that

Part of this effect may well be due to the disorder and squalor of the environment. Poor people and people of color are disproportionately exposed to “broken windows.”

It is interesting that the “broken windows” are considered to cause disease and health inequity. What happened first: the “broken windows,” or the lack of social skills and the abandonment of the population who live in such places? As a scientist, I find it very difficult to accept that “broken windows” are associated with the number of cases of gonorrhea and are associated with causality. The cases of venereal diseases (VD) are more related to the social skills and social behaviors of the people living in the community. They also have a lack of respect for property, and destruction of property often occurs.

If we say the reverse is plausible, what would happen if we got a grant and fixed all of the “broken windows” in a particular community, with no other intervention, and observed the trend of VD? With the assumptions and inferences made in Frumkin’s editorial, this would have a positive effect in reducing cases of VD. My instincts tell me that this would not be the case. The “broken windows” are a consequence of the behaviors of that particular community and they are not the cause of the behaviors. The “broken windows” are what I consider “collateral damage” of people lacking the necessary social skills to overcome certain challenges, such as socioeconomic stress and the lack of maintenance provided by building owners. These people show their frustration and anger many times against property, as well as other people.

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## “Broken Windows”: Frumkin Responds

I thank Meléndez for his careful reading of my editorial and for raising the very reasonable question of whether “broken windows”—an indicator of neighborhood squalor—are causally related to poor health.

Clearly the relationship between features of the built environment—including signs of degradation and outcomes such as behavior and health—is very complex. Many of the causal arrows are probably bidirectional. True clinical trials, which might help disentangle and clarify specific causal pathways, are difficult to carry out, as Meléndez points out. However, at least two interesting studies approximate a trial and are informative.

First, in the mid-1990s, former New York City police commissioner William Bratton implemented a “fixing broken windows” approach—enforcing nuisance laws, cleaning up graffiti, and so on. This approach was credited with a substantial subsequent decrease in street crime (Bratton 1995; Bratton and Knowlner 1998; Kelling and Coles 1996). Second, the Moving to Opportunity trial in the mid-1990s enrolled over 3,000 families in high-poverty neighborhoods of Baltimore, Maryland; Boston, Massachusetts; Chicago, Illinois; Los Angeles, California; and New York, New York. They were randomly assigned to receive housing vouchers usable in low-poverty neighborhoods or to remain where they were. Although the results were variable, families moving to low-poverty neighborhoods did experience improvements in several aspects of physical and mental health (Orr et al. 2003). So while these effects are not simple, there is some evidence that less-chaotic, disordered environments may predict better health.

Perhaps the fundamental issue is that in poor communities, environmental factors and social factors are inextricably intertwined. Our efforts to understand their effects on health, and to improve people’s lives, need to focus on the root causes of both poverty and environmental hazards.

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## Toxicity Tests: “Inert” and Active Ingredients

The findings of Richard et al. (2005) are an important addition to our understanding that the health and environmental effects of formulated pesticide products are not fully reflected in tests conducted on the active ingredient(s) alone. It has been long known that the adjuvants (commonly and misleadingly called “inert” ingredients) may be toxic and may enhance or supplement the toxic effects of the active pesticidal ingredient.

In the case of glyphosate-containing products, this phenomenon was well demonstrated in the data submitted to the (EPA) by the registrant (Monsanto), and summarized by the U.S. EPA in the Reregistration Eligibility Document (RED) for glyphosate (U.S. EPA 1993). For example, based on the registrant’s own tests of acute toxicity to freshwater fish, the U.S. EPA classified technical grade glyphosate as “slightly toxic” to “practically non-toxic” and formulated products ranged from “moderately toxic” to “practically non-toxic.” Tested alone, the surfactant adjuvant (identified as “inert”) was “highly toxic” to “slightly toxic.” Similar differences were reported in tests of acute toxicity to freshwater invertebrates.

Based in part on the data in the glyphosate RED (U.S. EPA 1993), the New York State Attorney General’s office successfully pursued an action against Monsanto in 1996 (Attorney General of the State of New York 1996). At that time, Monsanto was making advertising claims about the toxicity of the Roundup products based on data from tests on the active ingredient alone. Such claims are scientifically unfounded and inherently deceptive. The Attorney General’s action was facilitated by the availability of at least some limited information about the inert ingredients and their toxicity. That same sort of information enabled Richard et al. (2005) to conduct their study.

Unfortunately, that is not always the case, and for many pesticide products, little

or no information about the identity of inert ingredients is publicly available. Registrants are generally required to conduct acute toxicity tests on formulated products, but they traditionally conduct chronic toxicity tests on the active ingredient alone. Even when formulated products are tested, the identity of inert ingredients is rarely revealed in the open literature, publicly available regulatory documents, or product labels. Therefore, independent research is stymied, and the public is ill-informed in the marketplace.

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### "Inert" and Active Ingredients: Seralini Responds

Surgan raises interesting points in his analysis. This interest has been confirmed by reactions of agriculture authorities all over the world after publication of the article by Richard et al. (2005).

Indeed, scientific problems do exist in the registration of pesticides today, when chronic toxicity tests are conducted with the active ingredient alone—which is generally the case. First of all, chemists from companies may work hard for several years to find the right formulation that best amplifies the effects of the active ingredient. his formulation will allow penetration and stability and/or bioaccumulation of the active ingredient within plant, fungi, or insect cells, for instance, to reach the best toxicity. If there are any side effects in other animal or human cells, these will be also amplified by adjuvants, and thus not measured in chronic toxicity tests with the active ingredient alone. The active compound absorption by skin is generally calculated in the presence of formulated adjuvants, but this is clearly a short-term study and not sufficient to detect, for example, endocrine disruption or carcinogenesis, possibly promoted *in vivo*

by the described synergy. This should even necessitate further care in case of the use of formulated products such as glyphosate-based herbicides on tolerant, edible plants.

As a matter of fact, most genetically modified crops have been modified and selected only to tolerate high-formulated herbicide absorption, but the plants are not submitted for registration requiring chronic toxicity studies involving long-term feeding of animals. Moreover, in the case of environmental pollution, active pesticide ingredients may encounter detergents or other lipophilic xenobiotics with comparable effects other than those of their own adjuvants, for instance, forming microvesicles to penetrate the cells. These combined effects should also be taken into account in authorized thresholds of pollution in order to avoid effects on wildlife or humans.

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